REMARKS

1. Introduction

1.1. The instant office action is identified as final in the office action summary. However, it was the first action on the merits of the application, which is not a continuing application, and hence finality on the first action was not proper. See MPEP 706.07(b).

We were advised by the Examiner on April 6, 2004 that the indication of finality was inadvertent and erroneous; this case, she said, is "definitely a nonfinal action".

Checking this case on Public PAIR on September 16, 2004, we confirmed that the March 18, 2004 action is now identified as a "Non-Final Rejection", and hence we assume that we do not need to take further action to compel withdrawal the erroneous identification of finality. However, the Examiner should acknowledge the error in the next action to complete the record.

1.2. On July 20, 2004, the Examiner mailed a restriction requirement which, while it quoted the serial number of the present case, was plainly directed to a different case with related subject matter. On July 27, we filed a request to vacate. The Examiner is respectfully requested to clarify the record by vacating that restriction when she acts on this amendment.

2. Claims and Specification

2.1. In the last action, claims 1, 2, 5, 8-10, 19, 20, 22 and 23 were rejected. Claims 3, 4, 6, 7, 12-18, 21 and 24 are pending but withdraw from consideration on the basis of the October 2, 2003 restriction, as finalized March 19, 2004.

By this amendment, claims 1-6, 12, 13, 16-18, and 20 are amended, claims 8-11, 19, 21 and 22, are cancelled, and claims 25-43 are added.

Claim 1, as examined, contemplated administration of "α-MSH and/or of an α-MSH equivalent and/or... EPO and/or an EPO equivalent". As amended, claim 1 no longer recites "α-MSH", an "α-MSH equivalent" or an "EPO equivalent", and administration of EPO is mandatory. Claim 1 also incorporates the limitation of former claim 19.

Dependent claims recite additional administration of "α-MSH" (claims 26-27), or of an "α-MSH equivalent" (claims 28-37, 41-43) as specially defined.

New claims 28-37 and 41-43 are based on the teachings of pp. 16-17, and the references cited therein. The last paragraph of P16 cites various references on α-MSH equivalents, and these references are incorporated by reference on page 38.

28: P17, L2 and P16 (WO88/00833; USP 5,028,592)
29: P17, L2
30: P17, L3
31: P16 (WO96/41815 and USP 5,830,994)
32: same, including "X" to complete 4 aa fragment
33: same, including "Y" to complete 4 aa fragment
34: P17, L3; in view of WO96/41815 and USP 5,830,994
35: as above
36: P16 (WO88/00833 and USP 5,028,592)
37: P16 (WO99/21571)
38: P16 (WO87/04623)
41: see 28
42: see 30
43: see 31

Claim 25 (asthma) is based on P5, L13.

The amendment to claim 20, relating to exacerbation of COPD is based on P5, L25-27.

Several unelected claims have been amended but these amendments are not discussed herein as they are moot unless those

claims are rejoined.

2.2. Since the references on page 16 are incorporated by reference on page 38, the specification can be amended to explicitly recite their teachings without adding "new matter".

3. Prior Art Issues

3.1 Anticipation by Delgado-Hernandez (claims 1, 19, 22, 23)

According to the Examiner, Delgado Hernandez et al teach that LPS-elevated lung myeloperoxidase, a marker of neutrophil infiltration...was reduced by administration of alpha-MSH".

The Examiner concedes on P12 that "Delgado Hernandez et al. do not teach the administration of EPO for a non-ischemic condition". Consistently, the Examiner did not reject former claim 10, requiring use of EPO and/or an EPO equivalent, as anticipated by Delgado-Hernandez et al. Hence, Delgado-Hernandez et al. does not anticipate amended claim 1, which requires administration of EPO.

3.2. Anticipation by Akamatsu (claims 1 and 9)

Akamatsu shows that human EPO may be used to treat anemia caused by malignant tumors, which is a non-ischemic condition.

The Examiner did not reject former claim 19, reciting that the condition is "characterized by inflammation of the lung or airways", as anticipated by Akamatsu.

As claim 1 has been amended to incorporate the limitation of claim 19, this rejection should be withdrawn.

3.3. Obviousness over Delgado Hernandez in view of Akamatsu (claims 1, 5, 9, 10)

Claim 1 has been amended to require EPO (cp. former claim 10) in treatment of an inflammation of the lung or airways (cp. former claim 19). Since claim 19 was not rejected for obviousness, the rejection is mooted by this amendment.

4. Enablement/Description

4.1. "Prevent"

The Examiner assumes that the term "prevent", as used in the claims, should be interpreted as meaning total protection, i.e., the disease will occur in any individual receiving prophylaxis. The Examiner then declares that a very high degree of evidence is required for the art to accept that total protection is provided. We traverse.

It is routine in the medical field to refer to a treatment as "preventing" a disease because there is a statistically significant difference in subsequent incidence of the disease in the treatment group relative to the control group. Moreover, the literature will sometimes refer to a "percent prevention".

It is clear we are using the term in a relative sense because we assert 89% prevention at P38, L2 and 80% at P38, L4.

It should also be noted that even where "percent prevention" applies, there is absolute prevention in a given individual of a given incident.

In order to expedite prosecution, in claims 1-4, we have replaced "prevention" with --prophylaxis--. Also, we have added claims (39-43) limited to treatment.

4.2. "Equivalents"

The Examiner also says that there is a lack of enablement and written description for "alpha-MSH equivalents" and "EPO equivalents".

4.2.1. This rejection is moot as applied to EPO equivalents. Applicants assume that the term "erythropoietin", as used herein, would encompass the various natural forms of erythropoietin. USP 5,986,047, at col. 1, lines 23-38, discloses several such forms (alpha, beta, and their asialo derivatives).

4.2.2. The "alpha-MSH equivalents", are now identified both structurally and functionally. For example, in claim 28, it is

a peptide comprising the amino acid motif Lys-Pro-Val which acts on an alpha-MSH receptor and/or a melanocortin receptor and thereby has anti-inflammatory activity". The receptor targeting limitation is derived from original claim 8 and see also P16, L31-32. Claim 29 recites Gly-Lys-Pro-Val, per P17, L2. Claim 30 recites His-Phe-Arg, per P17, L3. The "His-Phe-Arg" motif is disclosed at P17, L2. Claims 31-38 are based wholly or partially on the disclosures of the alpha-MSH equivalents references cited on page 16 incorporated by reference on page 38.

Most studies point to the fact that the anti-inflammatory effects of αMSH- and αMSH analogues is due to melanocortin type 1 receptor (MC1) activation. Studies by molecular modelling of the MC1 receptor or docking of small cyclic MSH structures have shown that the sequence centered around amino acid 6-9 (His-Phe-Arg-Trp) represents the core message for binding of melanocortins to the melanocortin receptors. For a review please see Wikberg et al; Pharm Research 42:393-420, 2000, figure 4 page 405 (enclosed). In addition to this, studies have shown that it is possible to make substitutions of Phe within this 4 amino acid structure with either D-Phe or D-Nal and still have marked affinity against the MC1 receptor (for a review please see Wikberg et al: Pharm research 42:393-420, 2000).

4.3. The Examiner also says that the specification is not enabled for all non-ischemic conditions because they are too diverse.

It is believed that this rejection is mooted by the incorporation of the limitations of claim 19.

4.4. Finally, the examiner asserts that there is a lack of enablement for treatment or prevention of chronic obstructive pulmonary disease.

COPD is a chronic disease associated with exacerbation, which clinically can be defined as a complex of respiratory symptoms (i.e. new onset or worsening of more than one symptom

such as cough, sputum, dyspnea or wheeze) lasting for at least 3 days. Many patients with COPD experience recurrent exacerbations that significantly contribute to a more rapid decline in lung function, morbidity and poorer quality of life as well as to increased healthcare costs (Respir Med 98:883-91, 2004, enclosed).

The model of acute lung inflammation induced by LPS inhalation is widely used as a model for COPD, as evidenced by more than 100 published papers using the model. Experimentally LPS inhalation induces an inflammatory response with neutrophil and eosinophil infiltrations that mimics the inflammatory response seen during an exacerbation in COPD (Am. J. Respir. Crit. Care Med. 150:1646-1652, 1994).

The inventors therefore believe that the described effects of EPO optionally in combination with aMSH (or a MSH equivalent) are predictive for a protective effect of the compounds against exacerbations in COPD.

5. Sequence Listing

In the course of preparing this response it was discovered that a tetrameric peptide sequence on P17, L2 had been overlooked. This tetramer is a fragment of alpha-MSH. The specification has been amended to identify the α-MSH sequence as SEQ ID NO:1, and the tetrameric sequence in question as a fragment of SEQ ID NO:1, and the tetrameric sequence in question as a fragment of SEQ ID NO:1, and the Sequence Listing paper copy and CRF are enclosed.

Note that the trimeric peptide sequences on P17, L1-3 do not require listing. Also, the sequence rules do not require listing of peptides containing D-amino acids, or sequences with fewer than four specifically defined amino acids, see MPEP 2422.01.

5.1. Applicants hereby submit the following:

a paper copy of a "Sequence Listing", complying with

§1.821(c), to be incorporated into the specification; the Sequence Listing in computer readable form, complying with §1.821(e) and §1.824, including, if an amendment to the paper copy is submitted, all previously submitted data with the amendment incorporated therein.

5.2. The description has been amended to comply with §1.821(d).

5.3. The undersigned attorney or agent hereby states as follows:

(a) this submission does not include new matter [§1.821(g)];

(b) the contents of the paper copy (as amended, if applicable) and the computer readable form of the Sequence Listing, are the same [§1.821(f) and §1.825(b)];

(c) if the paper copy has been amended, the amendment is supported by the specification and does not include new matter [§1.825(a)]; and

(d) if the computer readable form submitted herewith is a substitute for a form found upon receipt by the PTO to be damaged or unreadable, that the substitute data is identical to that originally filed [§1.825(d)].

5.4. Under U.S. rules, each sequence must be classified in <213> as an "Artificial Sequence", a sequence of "Unknown" origin, or a sequence originating in a particular organism, identified by its scientific name.

Neither the rules nor the MPEP clarify the nature of the relationship which must exist between a listed sequence and an organism for that organism to be identified as the origin of the sequence under <213>.

Designation of a sequence as "artificial" should not be construed as a representation that the sequence has no association with any organism. For example, a primer or probe may be designated as "artificial" even though it is necessarily complementary to some target sequence, which may occur in nature. Or an "artificial" sequence may be a substitution mutant of a natural sequence, or a chimera of two or more natural sequences, or a cDNA (i.e., intron-free sequence) corresponding to an intron-containing gene, or otherwise a fragment of a natural sequence.

The Examiner should be able to judge the relationship of the enumerated sequences to natural sequences by giving full consideration to the specification, the art cited therein, any further art cited in an IDS, and the results of his or her sequence search against a database containing known natural sequences.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By: _____
Iver P. Cooper
Reg. No. 28,005

Enclosures
-Sequence Listing (paper and CRF)

624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone: (202) 628-5197
Facsimile: (202) 737-3528
IPC:lms
G:\ipc\n-q\Plou\nielsen3b\ptoamend.wpd